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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/611,363	07/01/2003	John R. Desjarlais	067461-5105-US01	4995

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EXAMINER

DEBERRY, REGINA M

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1647

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/611,363	Applicant(s) DESJARLAIS ET AL.	
	Examiner Regina M. DeBerry	Art Unit 1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 22 March 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-33 is/are pending in the application.
- 4a) Of the above claim(s) 27,28,31 and 33 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-26,29,30 and 32 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

Status of Application, Amendments and/or Claims

The amendment filed 22 March 2007 has been entered in full. Claims 1-33 are pending. Applicant's argument regarding the withdrawal of claims 2, 4, 12, 14, 17, 19, 22 and 24 (as set forth in Office Action date 22 September 2006; page 2) was found persuasive. Claims 2, 4, 12, 14, 17, 19, 22 and 24 will be examined.

Applicant traverses the withdrawal of claim 31. Applicant argues that the modifications in claim 31 refer to point mutations. Applicant argues that claim 31 recites modifications such as PEGylation, glycosylation and fusion to another entity that do not entail substitution of one amino acid for another. Applicant's arguments have been fully considered but are not found persuasive because it is unclear what the claim limitation "and fusion of said variant protein to another entity" encompasses. Due to the lack of guidance in the specification, the Examiner has interpreted the limitation "and fusion of said variant protein to **another entity**" to encompass any type of modification and thus does not read on the elected variants.

Claims 27, 28, 31 and 33 remain withdrawn from further consideration. Claims 1-26, 29, 30 and 32 are under examination.

Withdrawn Objections And/Or Rejections

The specification is in compliance with 37 CFR 1.821-1.825 of the Sequence Rules and Regulations.

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The rejection to claims 1, 3, 5-11, 13, 15, 16, 18, 20, 21, 23, 25, 26, 29, 30 and 32 under 35 U.S.C. 112, second paragraph, as set forth at page 8 of the previous Office Action (22 September 2006), is *withdrawn* in view of the amendment (22 March 2007).

The objection to claim 3, as set forth at page 8 of the previous Office Action (22 September 2006), is *withdrawn* in view of the amendment (22 March 2007).

Claim Rejections - 35 U.S.C. § 112, First Paragraph, Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-26, 29, 30 and 32 (this includes newly joined claims 2, 4, 12, 14, 17, 19, 22 and 24) remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

a variant RANKL protein comprising an amino acid modification at C221S/I247E and at least position selected from the group consisting of: R223M, R223E, R223Q, H225T, H225N, H225E, H225R, E226Q, E226D, E226R, Q237T, Q237K, Q237E, E269R, E269T, E269Q and E269K,

does not reasonably provide enablement for:

a variant RANKL protein wherein said variant RANKL comprises the modifications as recited in the instant claims.

The basis for this rejection is set forth at pages 4-8 of the previous Office Action (22 September 2006). Applicant states that claim 1 was amended to recite a

modification at C221 and I247 and that claims 3-5, 13, 19, 23, 24, 26 and 28 were amended to recite substitutions C221S and I247E.

Applicant's arguments have been fully considered but are not deemed persuasive because the instant claims have not been amended to recite, "a variant RANKL protein comprising an amino acid modification at C221S/I247E, and at least one position selected from the group consisting of R223M, R223E, R223Q, H225T, H225N, H225E, H225R, E226Q, E226D, E226R, Q237T, Q237K, Q237E, E269R, E269T, E269Q and E269K". The purported utility of the instant invention is novel variants of human RANKL protein, which behave as RANKL antagonists or superagonists and have soluble expression in *E. coli*. The Examiner stated in the previous Office Action (22 September 2006), that only specific variant RANKL proteins were shown to exhibit solubility, inhibition of osteoclastogenesis with or without RANK receptor binding and/or inhibition of OPG binding. These types of changes are largely unpredictable as to which ones have a significant effect versus not. The instant specification teaches specific variant RANKL proteins, which are suitable. Therefore, the RANKL variant proteins, as recited in the instant claims, result in an unpredictable and therefore unreliable correspondence between the claimed biomolecule and the indicated similar biomolecule of known function and therefore lacks support regarding enablement.

Applicant argues against the rejection to claim 32 (a pharmaceutical composition comprising a variant RANKL protein according to claim 1 and a pharmaceutical carrier). Applicant states that Freshney (reference cited by Examiner) does not teach, explicitly or implicitly, that binding studies of a compound carried out *in vitro* cannot be correlated

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to a therapeutic effect *in vivo*. Applicant argues that in the 19 years between publication of the Freshney reference and the application's 2002 effective filing date, both the law and the art have come to recognize that *in vitro* assays are a valuable tool for identifying compounds that exhibit a pharmacological and therapeutic effect. Applicant cites MPEP 2107.03(I), original emphasis; citing *Cross v. Iizuka*, 753 F.2d 1040 (Fed. Cir. 1985) and MPEP 2164.03 (citing *In re Fisher*, 427 F.2d 833 (CCPA 1970)). Applicant argues that the use of RAW 264.7 cells in a TRAP assay to identify compounds that therapeutically block osteoclastogenesis is well known in the art. Applicant argues that the specification of the present applicant has already clearly incorporated references from the art that set out the correlation between RAW 264.7 assays and the determination of osteoclastogenesis inhibition. Applicant cites Wang et al. Applicant argues that Wang et al. used RANKL-induced RAW 264.7 cells to assess the effect of a compound on osteoclastogenesis and note that selective modulation of RANKL signaling pathways may have important implications for the treatment of bone disease associated with enhanced bone resorption. Applicant cites McClung et al. Applicant argues that McClung et al. recently published Phase 2 data demonstrating that injections of denosumab (a monoclonal antibody known to bind RANKL blocking the interaction of RANKL with RANK), significantly increased bone mineral density in a group of postmenopausal women. Applicant argues that the Federal Circuit requires only a reasonable correlation between an *in vitro* assay and *in vivo* activity to demonstrate therapeutic utility. Applicant argues that Wang, McClung and references cited in the

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specification indicate that *in vitro* assays of proteins affecting RANKL binding reasonably correlate such protein with a pharmacological effect.

Applicant's arguments have been fully considered but are not found persuasive. In response to Applicant's argument regarding the age of the Freshney reference, contentions that the reference is old is not impressive absent a showing that the art tried and failed to solve the same problem notwithstanding its presumed knowledge of the references. See *In re Wright*, 569 F.2d 1124, 193 USPQ 332 (CCPA 1977).

In response to Applicant's arguments regarding Wang et al., Wang et al. teach that TPA inhibited RANKL-induced RAW 264.7 cell differentiation into osteoclast. Wang et al. state teach that given that NF-kB activation is obligatory for osteoclast differentiation, our studies imply that inhibition of osteoclastogenesis by TPA, is, at least in part caused by the suppression of RANKL-induced activation of NF-kB during an early stage of osteoclastogenesis. Wang et al. teach that selective modulation of RANKL signaling pathways by PKC activators may have important therapeutic implications for the treatment of bone diseases associated with enhanced bone resorption. Most importantly, Wang et al. teach that NF-kB signaling has been shown to play an important role in osteoclastogenesis. NF-kB p50^{-/-} and p52^{-/-} double knockout mice exhibit severe osteopetrosis caused by failure of osteoclast formation. NF-kB is activated by RANKL both in RAW 264.7 cells and in monocytes and is required for *in vivo* for osteoclast formation (Discussion, page 2165, 1st paragraph). Thus, unlike the instant specification, Wang et al. teaches the use of *in vivo* experiments in addition to the use of RAW 264.7 cells.

In response to the McClung et al. reference, McClung et al. state that the discovery of the RANKL-RANK pathway as the primary mediator of osteoclast differentiation, activation and survival facilitated the design of molecules that specifically target this pathway for the treatment of osteoporosis. McClung et al. state that by mimicking the effect of endogenous osteoprotegerin, denosumab, a fully human monoclonal antibody to RANKL, inhibited bone resorption with a rapid onset of action and a sustained but reversible effect. McClung cites a paper that describes treatment in postmenopausal women. Applicant argues that McClung et al. show that molecules that are known even before clinical trials and hence *in vitro* to have an effect on the RANKL-RANK pathway are the basis for designing molecules that can be used to treat osteoporosis. This argument is not found persuasive because McClung et al. did not stop with *in vitro* experiments. McClung et al. used *in vivo* experiments to demonstrate denosumab as a pharmaceutical composition. Furthermore, claim 13 reads on *in vivo* treatment/therapy not a method for designing molecules that could be used for *in vivo* treatment/therapy.

In response to Applicant's citation of MPEP 2107.03(I), original emphasis; citing *Cross v. Iizuka*, 753 F.2d 1040 (Fed. Cir. 1985), the instant citation discusses the precedent governing the utility requirement. The Examiner takes no issue with the utility of the instant invention. The issue regards the enablement of the instant invention. Furthermore the Examiner takes no issue with MPEP 2164.03 (citing *In re Fisher*, 427 F.2d 833 (CCPA 1970), which discusses the relationship of predictability of the art and the enablement requirement. Undue experimentation is a conclusion reached by

weighing all of the Wands factors. If one skilled in the art can readily anticipate the effect, then there is predictability in the art. In this case, however, the art is unpredictable based on the evidence provided. The evidence for the degree of predictability in the art also relates to the amount of direction needed in the specification. The instant claims read on the use of the instant composition for treatment/therapy. The instant specification fails to teach the pharmaceutical use within an animal to which the compound is administered for the prevention, diagnosis, alleviation, treatment, or cure of disease. Without sufficient guidance with respect to dosages and lack of working examples, leads to the conclusion that it would require undue experimentation to use the invention. A considerable amount of time is permissible for the quantity of experimentation needed to make or use the invention based on the disclosure. However this depends on if the invention is routine or if the skilled artisan is given sufficient direction or guidance. In the instant case, the experimentation is not routine and the specification has provided little or no guidance.

The scientific reasoning and evidence as a whole indicates that the rejection should be maintained.

NEW CLAIM REJECTIONS/OBJECTIONS

Claim Objections

Claims 1, 11, 12, 16, 17, 21, 22 and 25 are objected to because of the following informalities: The instant claims are objected to because of the recitation, "and at at least one position". Appropriate correction is required.


Conclusion


No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Regina M. DeBerry whose telephone number is (571) 272-0882. The examiner can normally be reached on 9:00 a.m.-6:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol can be reached on (571) 272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.


RMD
5/30/07


MARIANNE P ALLEN
PRIMARY EXAMINER

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